PHARMACEUTICAL COMPOSITION OF ANTIVIRAL AGENTS

Related Applications

This application claims priority to European Application No. 03029526.5, filed December 20, 2003; European Application No. 03016226.7, filed July 17, 2003; and European Application No. 03006996.7, filed March 27, 2003, each of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition useful for the treatment of viral infections comprising nevirapine and at least one antiviral active compound of formula (I). Furthermore the present invention relates to a use of nevirapine in combination or alternation with a compound of formula (I) in the prophylaxis or treatment of a viral infection in a patient. The present invention also relates to a use of nevirapine in combination with a compound of formula (I) for the manufacture of a medicament for the prophylaxis or treatment of a viral infection in a patient. In addition the present invention relates to a kit of parts and to a manufacture for the prophylaxis or treatment of a viral infection in a patient.

BACKGROUND OF THE INVENTION

Human immunodeficiency virus (HIV) is recognized as the causative agent in AIDS.

Current therapies for HIV infection focus on inhibiting the activity of viral enzymes which are essential to the life cycle of the virus. The agents that are presently in use fall mainly into three classes, designated Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs), and Protease Inhibitors (PIs). Presently, combination therapies, i.e. the

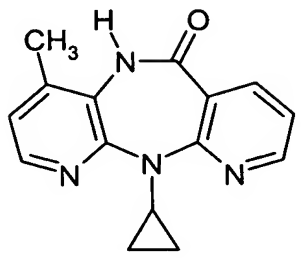
selection of two or more antiretroviral agents taken together to make up a "drug cocktail," are the preferred treatment for HIV infection. Combination therapies have been shown to reduce the incidence of opportunistic infections and to increase survival time. Typically, the drug cocktail combines drugs from different classes, so as to attack the virus at several stages in the replication process. This approach has been shown to reduce the likelihood of the development of virus forms that are resistant to a given drug or class of drugs.

Treatment failure with rebound of the amount of HIV which can be measured in the blood is common for patients treated with combination antiretroviral regimens. Resistance to the drugs in the drug regimen develops as the virus replicates in the presence of these drugs. Because of structural similarities of the drugs within an antiretroviral class, cross resistance is commonly seen to the other members of that class (for example virologic failure on a regimen containing an NNRTI will lead to cross resistance to the other first generation NNRTI agents). As patients experience repeated virologic failure on antiretroviral combination therapy, their viruses develop broad multi-class antiretroviral drug resistance which limits the effectiveness of the next round of antiretroviral therapy. Many highly treatment experienced patients have been exposed to all three classes of antiretroviral drugs and cannot obtain two active drugs to form the core of a new, effective antiretroviral drug regimen.

Nevirapine (Viramune®) is a non-nucleoside inhibitor of HIV reverse transcriptase, which is useful in the treatment of HIV infection in humans. The chemical name for nevirapine is

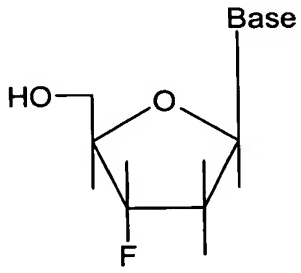
11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-

b:2',3'-e][1,4]diazepin-6-one. The structural formula of nevirapine is:



The earliest known synthesis of nevirapine, by Hargrave et al., is described in US Patent 5,366,972.

Furthermore compounds of the formula (I)

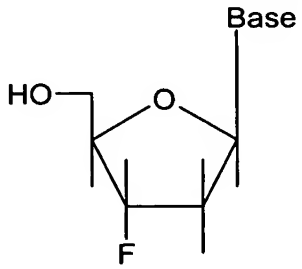


wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof, are described in the WO 88/00050 and WO 91/01137 for the therapeutic and prophylactic control and treatment of AIDS, HIV infections, hepatitis B virus (HBV) infections and retrovirus infections in animals and man. These nucleoside compounds are transformed by cells or enzymes to triphosphates which inhibit the reverse transcriptase of retrovirus as well as the activity of DNA dependent polymerase of hepatitis B virus.

Combinations of nevirapine with at least one compound of the formula (I) which exhibit potent therapeutic activity against HIV and HBV would greatly aid in the development of new combination therapy against human retroviral (HRV) infections and HBV.

SUMMARY OF THE INVENTION

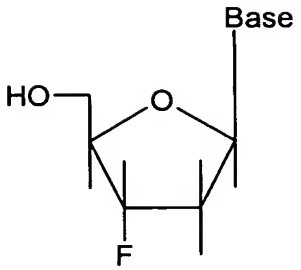
In one aspect, the present invention provides a novel pharmaceutical composition useful for the treatment or prophylaxis of viral infections comprising nevirapine and at least one antiviral active compound of formula (I)



wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof.

The pharmaceutical compositions of the present invention are useful in therapy, in particular as antivirals, especially in the treatment or prophylaxis of human retroviral (HRV) infections.

In a second aspect, there is provided a use of nevirapine in combination or alternation with at least one antiviral active compound of formula (I)



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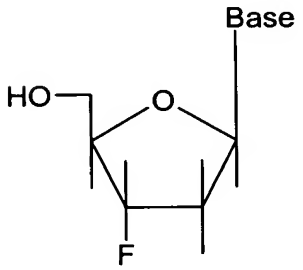
wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof, in the prophylaxis or treatment of a viral infection in a patient.

In a third aspect, there is provided a use of nevirapine in combination with at least one antiviral active compound of formula (I)



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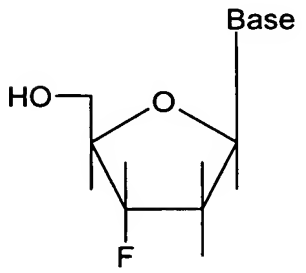
wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof, for the manufacture of a medicament for the prophylaxis or treatment of a viral infection in a patient.

In a fourth aspect of this invention, there is provided a kit of parts for the prophylaxis or treatment of a viral infection in a patient, comprising

(a) a first containment containing a pharmaceutical composition comprising nevirapine and at least one pharmaceutically acceptable carrier, and

(b) a second containment containing a pharmaceutical composition comprising an antiviral active compound of formula (I)



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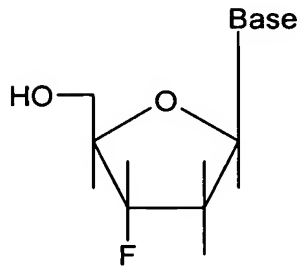
wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically acceptable salt or prodrug thereof, and at least one pharmaceutically acceptable carrier.

In a fifth aspect of this invention, there is provided a manufacture comprising nevirapine and at least one antiviral active compound of formula (I)



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wherein Base is selected from the group consisting of thymine, cytosine, adenine, guanine, inosine, uracil, 5-ethyluracil and 2,6-diaminopurine, or a pharmaceutically

acceptable salt or prodrug thereof, for use in combination or alternation in the prophylaxis or treatment of a viral infection in patient.

With the combination of nevirapine and a compound of the formula (I) according to this invention, including its use in prophylaxis and treatment, the person skilled in the art can achieve an advantageous therapeutic effect to inhibit viral replication, especially of human retrovirus (HRV) and HBV, in particular of multiresistant HIV. In most cases, the enhanced therapeutic effect is not attainable by administration of either agent alone. In a preferred but not necessary embodiment, the effect of administration of nevirapine and the compound of formula (I) in combination or alternation is synergistic. Even though a combination exhibits additive and not synergistic effects, the combination can still provide an effect that is different from the separate administration of the two agents. For example, the biodistribution, pharmacokinetics, cytotoxic effects or metabolism of one can be affected by the other.

Further aspects of the present invention become apparent to the one skilled in the art from the following detailed description and examples.

DEFINITIONS

The term "pharmaceutically acceptable salt" means a salt of the corresponding compound which is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, generally water or oil-soluble or dispersible, and effective for their intended use. The term includes pharmaceutically-acceptable acid addition salts and pharmaceutically-acceptable base addition salts. Lists of suitable salts are found in, e.g., S.M.

Birge et al., J. Pharm. Sci., 1977, 66, pp. 1-19, which is hereby incorporated by reference in its entirety.

As used herein, the term "treatment" means the administration of the antivirally active compounds according to this invention in combination or alternation according to the present invention to alleviate or eliminate symptoms of the viral infection and/or to reduce viral load in a patient.

As used herein, the term "prevention" or "prophylaxis" means the administration of the antivirally active compounds according to this invention in combination or alternation according to the present invention post-exposure of the individual to the virus but before the appearance of symptoms of the disease, and/or prior to the detection of the virus in the blood.

As used herein, the term "human retrovirus" (HRV) includes human immunodeficiency virus type I, human immunodeficiency virus type II, or strains thereof, as well as human T cell leukemia virus 1 and 2 (HTLV-1 and HTLV-2) or strains apparent to one skilled in the art, which belong to the same or related viral families and which create similar physiological effects in humans as various human retroviruses.

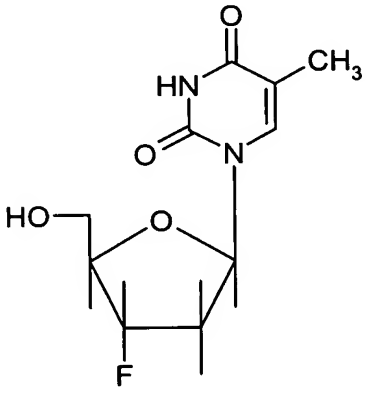
DETAILED DESCRIPTION OF THE INVENTION

The virally active agents according to this invention may be in either free form or in protected form at one or more of the remaining (not previously protected) carboxyl, amino, hydroxy, or other reactive groups. The protecting groups may

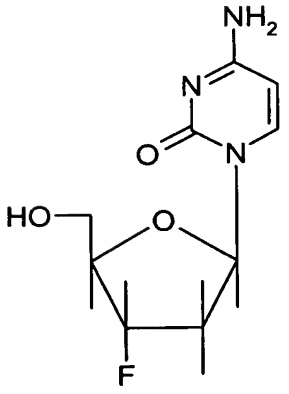
be any of those known in the art. Furthermore, the virally active agents according to this invention may also be used as in form of their pharmacologically acceptable salts and/or hydrates.

According to the first aspect of this invention, there is provided a novel pharmaceutical composition useful for the treatment of viral infections comprising nevirapine and at least one antiviral active compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof.

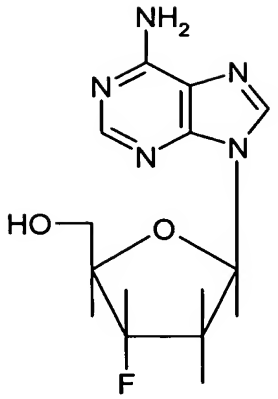
The following known compounds constitute part of the invention as preferred compounds of the formula (I) to be combined with nevirapine:



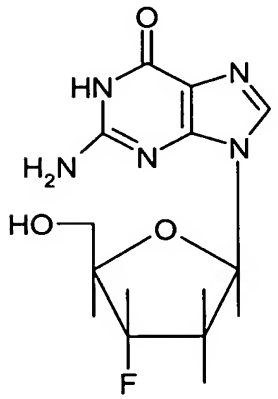
3'-deoxy-3'-fluorothymidine (FLT)



2',3'-dideoxy-3'-fluorocytidine



2',3'-dideoxy-3'fluoroadenosine



2',3'-dideoxy-3'-fluoroguanosine (FLG)

including pharmaceutically acceptable salts and prodrugs of the compounds listed above.

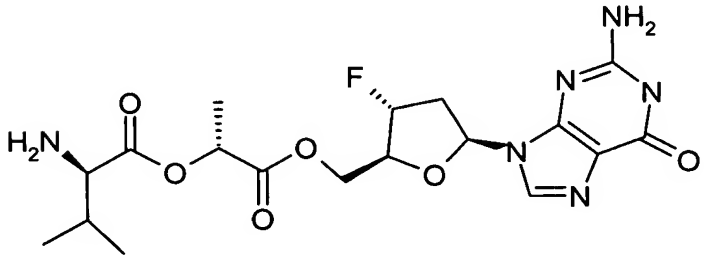
Preferred prodrugs of FLG are described in WO 99/09031 and WO 99/41268, which documents in their entirety are incorporated herein by reference.

The most preferred compound of the formula (I) to be combined with nevirapine according to the aspects of this invention is selected from the group consisting of
(a) 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, and
(b) 2',3'-dideoxy-3'-fluoroguanosine (FLG), or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-

propionyl]guanosine, or a pharmaceutically acceptable salt thereof.

The compound of the formula (I) is very most preferably selected from the group consisting of 3'-deoxy-3'-fluorothymidine and 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, including pharmaceutically acceptable salts thereof.

3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine is a preferred prodrug of FLG and can be depicted by the following structure:



The synthesis of 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, also named as 2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, is described in the WO 99/09031 and especially in example 32 therein.

Therefore, a preferred pharmaceutical composition useful for the treatment of viral infections comprises nevirapine and 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt or prodrug thereof.

Furthermore, nevirapine in combination or alternation with preferably 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt or prodrug thereof, is used

in the prophylaxis or treatment of a viral infection in a patient.

Also preferred is the use of nevirapine in combination with 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt or prodrug thereof, for the manufacture of a medicament for the prophylaxis or treatment of a viral infection in a patient.

A preferred kit of parts for the prophylaxis or treatment of a viral infection in a patient, comprises:
(a) a first containment containing a pharmaceutical composition comprising nevirapine and a pharmaceutically acceptable carrier, and
(b) a second containment containing a pharmaceutical composition comprising 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier.

A preferred manufacture comprises nevirapine and 3'-deoxy-3'-fluorothymidine or 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt or prodrug thereof, for use in combination or alternation in the prophylaxis or treatment of a viral infection in a patient.

The advantageous effects of the combination of nevirapine and the compound of formula (I) are realized over a wide ratio, like for example in a ratio of between 1:250 to 250:1.

Therefore, in the compositions, combinations, kit of parts, manufacture and/or the use of the combinations according to

this invention, nevirapine and the at least one compound of formula (I), which is preferably 3'-deoxy-3'-fluorothymidine, or a pharmaceutically acceptable salt or prodrug thereof, are preferably present in a synergistic ratio. Usually, this ratio is between about 1:250 to about 250:1. More preferably the ratio is between about 1:50 to about 50:1. The most preferred ratio is between about 1:20 to about 20:1, which includes the ratios 1:18, 1:16, 1:14, 1:12, 1:10; 1:8; 1:6; 1:5; 1:4; 1:3; 1:2,5; 1:2; 1:1,5; 1:1,2; 1:1; 1,2:1; 1,5:1; 2:1; 2,5:1; 3:1; 4:1; 5:1; 6:1; 8:1; 10:1, 12:1, 14:1, 16:1, 18:1 and all ranges in between. If a further therapeutic agent is added, ratios will be adjusted accordingly.

It will be appreciated that the amount of pharmaceutical composition according to the invention required for use in treatment or prophylaxis will vary not only with the particular compound selected but also with the route of administration, the nature and severity of the condition for which treatment or prophylaxis is required, the age, weight and condition of the patient, concomitant medication and will be ultimately at the discretion of the attendant physician or veterinarian. In general however the active compounds are included in the pharmaceutically acceptable carrier in an amount sufficient to deliver to a patient a therapeutically effective amount of compound to inhibit viral replication in vivo, especially HIV replication, without causing serious toxic effects in the treated patient. By "inhibitory amount" is meant an amount of active ingredient sufficient to exert an inhibitory effect as measured by, for example, an assay such as the ones described herein. A suitable dose will preferably be in the range of from about 0.05 to about 200 mg/kg of body weight per day.

The desired dose may conveniently be presented in a single dose or as divided dose administered at appropriate intervals, for example as two, three, four or more doses per day.

The pharmaceutical composition according to the present invention is conveniently administered in unit dosage form; for example containing 5 to 3000 mg, conveniently 5 to 1000 mg of active ingredient(s) per unit dosage form.

The pharmaceutical acceptable carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Examples of pharmaceutically acceptable carriers are magnesium stearate, chalk, starch, lactose, wax, gum or gelatin. Carriers which are suited to achieve a sustained release, for example natural or synthetic polymers or liposomes, are known to the one skilled in the art. Pharmaceutically acceptable carriers also comprise liquid carriers and diluents, for example water, alcohol, glycerine or oil, which serve as a base for liquid formulations, such as solutions, suspensions or emulsions.

The compositions referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and therefore pharmaceutical formulations comprising a composition as defined above together with a pharmaceutically acceptable carrier comprise a further aspect of the invention.

The individual components of such compositions may be administered either in combination, i.e. simultaneously, or in alternation, i.e. sequentially, in separate or combined pharmaceutical formulations.

When nevirapine is used in combination with a compound of the formula (I) against the same virus the dose of each compound may be either the same as or differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

The compositions according to this invention preferably also comprise at least one pharmaceutically acceptable carrier.

According to the third aspect of this invention, the combination of nevirapine and at least one compound of the formula (I) is used for the manufacture of a medicament for the prophylaxis or the treatment of a viral infection in a patient.

According to one embodiment, this medicament may be a unit dosage form, which is preferably useful in combination therapy, such as capsules or tablets. The unit dosage form contains a pharmaceutical composition according to this invention, i.e. nevirapine in combination with at least one compound of the formula (I), with at least one pharmaceutically acceptable carrier.

Therefore, another object of this invention also comprises bringing nevirapine and at least a compound of the formula (I) together in conjunction or association with a pharmaceutically acceptable carrier.

According to another embodiment, this medicament is a multiple dosage form, preferably a kit of parts, which is especially useful in alternation and/or combination therapy to flexibly suit the individual therapeutic needs of the patient.

According to further embodiments the combinations, compositions, kit of parts, manufactures of this invention and the uses thereof comprise a combination selected from the group consisting of:

- a compound of the formula (I), nevirapine and one, two or more further NRTIs;
- a compound of the formula (I), nevirapine, a protease inhibitor and optionally one, two or more further NRTIs;
- a compound of the formula (I), nevirapine, an entry inhibitor and optionally one, two or more further NRTIs;
- a compound of the formula (I), nevirapine, a protease inhibitor, an entry inhibitor and optionally one, two or more further NRTIs;
- a compound of the formula (I), nevirapine, a protease inhibitor, an integrase inhibitor and optionally one, two or more further NRTIs.

In the above listed combinations, compositions, kit of parts, manufactures and uses thereof a protease inhibitor may advantageously be combined with ritonavir in order to improve the pharmacokinetics of said protease inhibitor.

In the foregoing and in the following, the term "further NRTI" refers to a nucleoside reverse transcriptase inhibitor, or a pharmaceutically acceptable salt or prodrug thereof, other than the selected compound of the formula (I). Examples of further NRTIs are Abacavir Sulfate (Ziagen), Didanosine (ddI, Videx), Emtricitabine (Emtriva), Lamivudine (3TC, Epivir), Stavudine (d4t, Zerit), Tenofovir disoproxil fumarate (nucleotide, bis (POC) PMPA, Viread), Zalcitabine (ddc, Hivid), Zidovudine (AZT, Retrovir), Amdoxovir (DAPD; Gidead Sciences), Elvucitabine (ACH-126443; Achillion Pharm.), GS-7340 (Gilead Sciences), INK-20 (thioether phospholipid formulation of AZT; Kucera Pharm.), MIV-310 (Medivir AB), MIV-210 (Medivir AB), Racivir (racemic

FTC; Pharmasset), Reverset (RVT, D-D4FC, DPC-817; Pharmasset), SPD-754 ((-)dOTC; Shire Pharm), BCH-13520 (Shire Pharm) and BCH-10618 (Shire Pharm).

In the foregoing and in the following, the term "protease inhibitor" refers to a protease inhibitor, or a pharmaceutically acceptable salt or prodrug thereof. Examples of protease inhibitors are Amprenavir (VX-478, Agenerase), Atazanavir (Reyataz), Indinavir Sulfate (MK-639, Crixivan), Lexiva (fosamprenavir calcium, GW -433908 or 908, VX-175), Lopinavir + Ritonavir (ABT-378/r, Kaletra), Nelfinavir Mesylate (Viracept), Ritonavir (ABT-538, Norvir), Saquinavir (Invirase, Fortovase), Tipranavir + Ritonavir, AG-1776 (JE-2147, KNI-764; Nippon Mining Holdings), AG-1859 (Pfizer), DPC-681/684 (BMS), GS224338 (´4338; Gidead Sciences), KNI-272 (Nippon Mining Holdings), Nar-DG-35 (Narhex), P(PL)-100 (P-1946; Procyon Biopharma), P-1946 (Procyon Biopharma), R-944 (Hoffmann-LaRoche), RO-0334649 (Hoffmann-LaRoche), TMC-114 (Johnson & Johnson), VX-385 (GW-640385; GSK/Vertex) and VX-478 (Vertex/GSK).

In the foregoing and in the following, the term "entry inhibitor" refers to an entry inhibitor, including fusion inhibitors, inhibitors of the CD4 receptor, inhibitors of the CCR5 co-receptor and inhibitors of the CXCR4 co-receptor, or a pharmaceutically acceptable salt or prodrug thereof. Examples of entry inhibitors are AMD-070 (AMD-11070; AnorMed), BlockAide/CR (ADVENTRX Pharm.), BMS 806 (BMS-378806; BMS), Enfurvirtide (T-20, R698, Fuzeon), KRH-1636 (Kureha Pharmaceuticals), ONO-4128 (GW-873140, AK-602, E-913; ONO Pharmaceuticals), Pro-140 (Progenics Pharm), PRO-542 (Progenics Pharm.), SCH-D (SCH-417690; Schering-Plough), T-1249 (R724; Roche/Trimeris), TAK-220 (Takeda Chem. Ind.), TNX-355 (Tanox) and UK-427,857 (Pfizer).

Examples of integrase inhibitors are L-870810 (Merck & Co.), c-2507 (Merck & Co.) and S(RSC)-1838 (Shionogi/GSK).

According to still further embodiments the combinations, compositions, kit of parts, manufactures of this invention and the uses thereof comprise a combination selected from the group consisting of a compound of the formula (I), nevirapine and a further antiviral agent.

A further antiviral agent may be selected from the group of the maturation inhibitors, antisense compounds or NNRTIs, other than nevirapine. Examples of further antivirals are PA-457 (Panacos), KPC-2 (Kucera Pharm.), HGTV-43 (Enzo Biochem), Delavirdine (Rescriptor), Efavirenz (DMP-266, Sustiva), (+)- Calanolide A and B (Advanced Life Sciences), Capravirine (AG1549, S-1153; Pfizer), GW-695634 (GW-8248; GSK), MIV-150 (Medivir), MV026048 (R-1495; Medivir AB/Roche), NV-05 (Idenix Pharm.), R-278474 (Johnson & Johnson), RS-1588 (Idenix Pharm.), TMC-120/125 (Johnson & Johnson), TMC-125 (R-165335; Johnson & Johnson), UC-781 (Biosyn Inc.) and YM-215389 (Yamanoushi).

The combinations, compositions, kit of parts, manufactures of this invention and the uses thereof of the above mentioned embodiments may be combined with further active ingredients.

Examples of such further active ingredients are acyclic nucleosides such as acyclovir, ganciclovir; interferons such as alpha-, beta- and gamma-interferon; glucuronation inhibitors such as probenecid; nucleoside transport inhibitors such as dipyridamole; immunomodulators such as interleukin II (IL2) and granulocyte macrophage colony stimulating factor (GM-CSF), erythropoietin, ampligen, thymomodulin, thymopentin, foscarnet, glycosylation inhibitors such as 2-deoxy-D-glucose, castanospermine, 1-

deoxynojirimycin; and inhibitors of HIV binding to CD4 receptors such as soluble CD4, CD4 fragments, CD4-hybrid molecules and inhibitors of the HIV aspartyl protease such as L-735,524.

The compounds, or their pharmaceutically acceptable derivative or salts thereof, can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics, antifungals, antiinflammatorics, protease inhibitors, or other nucleoside or non-nucleoside antiviral agents, as discussed in more detail above.

In general, during alternation therapy, an effective dosage of each agent is administered serially, whereas in combination therapy, an effective dosage of two or more agents are administered together. The dosages will depend on such factors as absorption, biodistribution, metabolism and excretion rates for each drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions. Examples of suitable dosage ranges for nevirapine, compounds of formula (I), preferably 3'-deoxy-3'-fluorothymidine, further NRTIs and other antivirals can be found in the scientific literature. Many examples of suitable dosage ranges for other compounds described herein are also found in the public literature or can be identified using known procedures. These dosage ranges can be modified as desired to achieve a desired result.

It has been recognized that drug-resistant variants of HIV can emerge after prolonged treatment with an antiviral agent. Drug resistance most typically occurs by mutation of a gene that encodes for an enzyme used in the viral life cycle, and most typically in the case of HIV, in either the reverse transcriptase or protease genes. It has been demonstrated that the efficacy of a drug against HIV infection can be prolonged, augmented, or restored by administering the compound in combination or alternation with a second, and perhaps third, antiviral compound that induces a different mutation(s) from that selected for by the principle drug. Alternatively, the pharmacokinetics, biodistribution, or other parameter of the drug can be altered by such combination or alternation therapy. In general, combination therapy is typically preferred over alternation therapy because it induces multiple simultaneous stresses on the virus. In the case of administering the antiviral compounds in alternation, i.e. sequentially, the time gap between administering the first compound and the second compound is preferably not too long in order to achieve a beneficial effect. Preferably, the time gap is less than half a day, most preferably less than 6 hours.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation. The invention thus further provides a pharmaceutical formulation comprising nevirapine and a compound of the formula (I) with one or more pharmaceutically acceptable carriers and, optionally, other therapeutic and/or prophylactic ingredients.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration in liquid or

solid form or in a form suitable for administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound(s) with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Pharmaceutical formulation suitable for oral administration may conveniently be presented as discrete units such as capsules, including soft gelatin capsules, cachets or tablets each containing a predetermined amount of the active ingredient(s); as a powder or granules; as a solution, a suspension or as an emulsion, for example as syrups, elixirs or self-emulsifying delivery systems (SEDDS). The active ingredient(s) may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

The pharmaceutical composition according to the invention may also be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in

multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient(s) may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the active compound(s) with the softened or melted carrier(s) followed by chilling and shaping in moulds.

When desired the above described formulations adapted to give sustained release of the active ingredient(s) may be employed.

The compositions, combinations, kit of parts, manufacture and/or the use of the combinations according to this invention are advantageous in the treatment and/or prophylaxis of viral infections in a patient, preferably human retrovirus (HRV) infections and hepatitis B, in particular HIV infections, especially multiresistant HIV infections. Therefore this invention may offer an aid especially for highly treatment experienced patients suffering from multiresistant HIV. In addition to the treatment of said diseases, the combinations, formulations and compositions according to this invention can be used prophylactically to prevent or retard the progression of

clinical illness in individuals who are anti-HIV antibody or HIV-antigen positive or who have been exposed to HIV.

The compositions, combinations, kit of parts, manufacture and/or the use of the combinations according to this invention may also be beneficial in preventing perinatal transmission of human retroviral (HRV) infections, in particular HIV-1, from mother to baby. According to this method, nevirapine and a compound of the formula (I), preferably 3'-deoxy-3'-fluorothymidine, and optionally further active compounds as described hereinbefore or hereinafter are administered in combination or alternation to the mother before giving birth.

The compositions, combinations, kit of parts, manufacture and/or the use of the combinations according to this invention may also be beneficial in the treatment and/or prophylaxis of other HIV/AIDS-related conditions such as AIDS-related complex (ARC), persistent generalized lymphadenopathy (PGL), AIDS-related neurological conditions, anti-HIV antibody positive and HIV-positive conditions, Kaposi's sarcoma, thrombocytopenia purpurea and opportunistic infections.

Therefore, patients to be treated would be especially those individuals:

1) infected with one or more strains of a human retrovirus as determined by the presence of either measurable viral antibody or antigen in the serum; and/or

2) in the case of HIV, having either a asymptomatic HIV infection or a symptomatic AIDS defining infection such as i) disseminated histoplasmosis, ii) isopsoriasis, iii) bronchial and pulmonary candidiasis including pneumocystic pneumonia, iv) non-Hodgkin's lymphoma or v) Kaposi's sarcoma

and being less than sixty years old; or having an absolute CD4+ lymphocyte count of less than 500/mm³ in the peripheral blood.

The pharmaceutical combination according to this invention can be tested for additive and synergistic activity against HIV according to a number of assays known in scientific and public literature, including the one described in the WO 98/44913 and WO 00/51641, which are included herein by way of reference.

The present invention is illustrated in further detail by the following non-limiting examples of combinations according to this invention, comprising a 1st compound, a 2nd compound, optionally a 3rd compound, optionally a 4th compound and optionally a 5th compound.

Table 1 illustrating combinations of a compound of the formula (I), nevirapine and one, two or more further NRTIs

1st compound	2nd compound	3rd compound
FLT	Nevirapine	Abacavir Sulfate
FLT	Nevirapine	Didanosine
FLT	Nevirapine	Emtricitabine
FLT	Nevirapine	Lamivudine
FLT	Nevirapine	Stavudine
FLT	Nevirapine	Tenofovir disoproxil fumarate
FLT	Nevirapine	Zalcitabine
FLT	Nevirapine	Zidovudine

FLT	Nevirapine	Amdoxovir
FLT	Nevirapine	Elvucitabine
FLT	Nevirapine	GS-7340
FLT	Nevirapine	INK-20
FLT	Nevirapine	MIV-210
FLT	Nevirapine	Racivir
FLT	Nevirapine	Reverset
FLT	Nevirapine	SPD-754
FLT	Nevirapine	BCH-13520
FLT	Nevirapine	BCH-10618
FLG	Nevirapine	Abacavir Sulfate
FLG	Nevirapine	Didanosine
FLG	Nevirapine	Emtricitabine
FLG	Nevirapine	Lamivudine
FLG	Nevirapine	Stavudine
FLG	Nevirapine	Tenofovir disoproxil fumarate
FLG	Nevirapine	Zalcitabine
FLG	Nevirapine	Zidovudine
FLG	Nevirapine	Amdoxovir
FLG	Nevirapine	Elvucitabine
FLG	Nevirapine	GS-7340
FLG	Nevirapine	INK-20
FLG	Nevirapine	MIV-310
FLG	Nevirapine	Racivir

FLG	Nevirapine	Reverset
FLG	Nevirapine	SPD-754
FLG	Nevirapine	BCH-13520
FLG	Nevirapine	BCH-10618

Table 2 illustrating combinations of a compound of the formula (I), nevirapine, a protease inhibitor and optionally one, two or more further NRTIs

1st compound	2nd compound	3rd compound
FLT	Nevirapine	Amprenavir
FLT	Nevirapine	Atazanavir
FLT	Nevirapine	Indinavir Sulfate
FLT	Nevirapine	Lexiva
FLT	Nevirapine	Lopinavir + Ritonavir
FLT	Nevirapine	Nelfinavir Mesylate
FLT	Nevirapine	Ritonavir
FLT	Nevirapine	Saquinavir
FLT	Nevirapine	Tipranavir + Ritonavir
FLT	Nevirapine	AG-1776
FLT	Nevirapine	AG-1859
FLT	Nevirapine	DPC-681/684
FLT	Nevirapine	GS224338
FLT	Nevirapine	KNI-272

FLT	Nevirapine	Nar-DG-35
FLT	Nevirapine	P(PL)-100
FLT	Nevirapine	P-1946
FLT	Nevirapine	R-944
FLT	Nevirapine	RO-0334649
FLT	Nevirapine	TMC-114
FLT	Nevirapine	VX-385
FLT	Nevirapine	VX-478
FLG	Nevirapine	Amprenavir
FLG	Nevirapine	Atazanavir
FLG	Nevirapine	Indinavir Sulfate
FLG	Nevirapine	Lexiva
FLG	Nevirapine	Lopinavir + Ritonavir
FLG	Nevirapine	Nelfinavir Mesylate
FLG	Nevirapine	Ritonavir
FLG	Nevirapine	Saquinavir
FLG	Nevirapine	Tipranavir + Ritonavir
FLG	Nevirapine	AG-1776
FLG	Nevirapine	AG-1859
FLG	Nevirapine	DPC-681/684
FLG	Nevirapine	GS224338
FLG	Nevirapine	KNI-272
FLG	Nevirapine	Nar-DG-35

FLG	Nevirapine	P(PL)-100
FLG	Nevirapine	P-1946
FLG	Nevirapine	R-944
FLG	Nevirapine	RO-0334649
FLG	Nevirapine	TMC-114
FLG	Nevirapine	VX-385
FLG	Nevirapine	VX-478

Table 3 illustrating combinations of a compound of the formula (I), nevirapine, an entry inhibitor and optionally one, two or more further NRTIs

1st compound	2nd compound	3rd compound
FLT	Nevirapine	Enfurvirtide
FLT	Nevirapine	T-1249
FLT	Nevirapine	AMD-070
FLT	Nevirapine	BlockAide/CR
FLT	Nevirapine	BMS 806
FLT	Nevirapine	KRH-1636
FLT	Nevirapine	ONO-4128
FLT	Nevirapine	Pro-140
FLT	Nevirapine	PRO-542
FLT	Nevirapine	SCH-D
FLT	Nevirapine	TAK-220
FLT	Nevirapine	TNX-355
FLT	Nevirapine	UK-427,857
FLG	Nevirapine	Enfurvirtide

FLG	Nevirapine	T-1249
FLG	Nevirapine	AMD-070
FLG	Nevirapine	BlockAide/CR
FLG	Nevirapine	BMS 806
FLG	Nevirapine	KRH-1636
FLG	Nevirapine	ONO-4128
FLG	Nevirapine	Pro-140
FLG	Nevirapine	PRO-542
FLG	Nevirapine	SCH-D
FLG	Nevirapine	TAK-220
FLG	Nevirapine	TNX-355
FLG	Nevirapine	UK-427,857

Table 4 illustrating combinations of a compound of the formula (I), nevirapine, a protease inhibitor, an entry inhibitor and optionally one, two or more further NRTIs

1st compound	2nd compound	3rd compound	4th compound
FLT	Nevirapine	Amprenavir	Enfurvirtide
FLT	Nevirapine	Amprenavir	T-1249
FLT	Nevirapine	Amprenavir	AMD-070
FLT	Nevirapine	Amprenavir	BlockAide/CR
FLT	Nevirapine	Amprenavir	BMS 806
FLT	Nevirapine	Amprenavir	KRH-1636
FLT	Nevirapine	Amprenavir	ONO-4128

FLT	Nevirapine	Amprenavir	Pro-140
FLT	Nevirapine	Amprenavir	PRO-542
FLT	Nevirapine	Amprenavir	SCH-D
FLT	Nevirapine	Amprenavir	TAK-220
FLT	Nevirapine	Amprenavir	TNX-355
FLT	Nevirapine	Amprenavir	UK-427,857
FLT	Nevirapine	Atazanavir	Enfurvirtide
FLT	Nevirapine	Atazanavir	T-1249
FLT	Nevirapine	Atazanavir	AMD-070
FLT	Nevirapine	Atazanavir	BlockAide/CR
FLT	Nevirapine	Atazanavir	BMS 806
FLT	Nevirapine	Atazanavir	KRH-1636
FLT	Nevirapine	Atazanavir	ONO-4128
FLT	Nevirapine	Atazanavir	Pro-140
FLT	Nevirapine	Atazanavir	PRO-542
FLT	Nevirapine	Atazanavir	SCH-D
FLT	Nevirapine	Atazanavir	TAK-220
FLT	Nevirapine	Atazanavir	TNX-355
FLT	Nevirapine	Atazanavir	UK-427,857
FLT	Nevirapine	Indinavir Sulfate	Enfurvirtide
FLT	Nevirapine	Indinavir Sulfate	T-1249
FLT	Nevirapine	Indinavir Sulfate	AMD-070
FLT	Nevirapine	Indinavir Sulfate	BlockAide/CR

FLT	Nevirapine	Indinavir Sulfate	BMS 806
FLT	Nevirapine	Indinavir Sulfate	KRH-1636
FLT	Nevirapine	Indinavir Sulfate	ONO-4128
FLT	Nevirapine	Indinavir Sulfate	Pro-140
FLT	Nevirapine	Indinavir Sulfate	PRO-542
FLT	Nevirapine	Indinavir Sulfate	SCH-D
FLT	Nevirapine	Indinavir Sulfate	TAK-220
FLT	Nevirapine	Indinavir Sulfate	TNX-355
FLT	Nevirapine	Indinavir Sulfate	UK-427,857
FLT	Nevirapine	Lexiva	Enfurvirtide
FLT	Nevirapine	Lexiva	T-1249
FLT	Nevirapine	Lexiva	AMD-070
FLT	Nevirapine	Lexiva	BlockAide/CR
FLT	Nevirapine	Lexiva	BMS 806
FLT	Nevirapine	Lexiva	KRH-1636
FLT	Nevirapine	Lexiva	ONO-4128
FLT	Nevirapine	Lexiva	Pro-140
FLT	Nevirapine	Lexiva	PRO-542
FLT	Nevirapine	Lexiva	SCH-D

FLT	Nevirapine	Lexiva	TAK-220
FLT	Nevirapine	Lexiva	TNX-355
FLT	Nevirapine	Lexiva	UK-427,857
FLT	Nevirapine	Lopinavir + Ritonavir	Enfurvirtide
FLT	Nevirapine	Lopinavir + Ritonavir	T-1249
FLT	Nevirapine	Lopinavir + Ritonavir	AMD-070
FLT	Nevirapine	Lopinavir + Ritonavir	BlockAide/CR
FLT	Nevirapine	Lopinavir + Ritonavir	BMS 806
FLT	Nevirapine	Lopinavir + Ritonavir	KRH-1636
FLT	Nevirapine	Lopinavir + Ritonavir	ONO-4128
FLT	Nevirapine	Lopinavir + Ritonavir	Pro-140
FLT	Nevirapine	Lopinavir + Ritonavir	PRO-542
FLT	Nevirapine	Lopinavir	SCH-D

		+ Ritonavir	
FLT	Nevirapine	Lopinavir + Ritonavir	TAK-220
FLT	Nevirapine	Lopinavir + Ritonavir	TNX-355
FLT	Nevirapine	Lopinavir + Ritonavir	UK-427,857
FLT	Nevirapine	Nelfinavir Mesylate	Enfurvirtide
FLT	Nevirapine	Nelfinavir Mesylate	T-1249
FLT	Nevirapine	Nelfinavir Mesylate	AMD-070
FLT	Nevirapine	Nelfinavir Mesylate	BlockAide/CR
FLT	Nevirapine	Nelfinavir Mesylate	BMS 806
FLT	Nevirapine	Nelfinavir Mesylate	KRH-1636
FLT	Nevirapine	Nelfinavir Mesylate	ONO-4128
FLT	Nevirapine	Nelfinavir Mesylate	Pro-140
FLT	Nevirapine	Nelfinavir Mesylate	PRO-542
FLT	Nevirapine	Nelfinavir	SCH-D

		Mesylate	
FLT	Nevirapine	Nelfinavir Mesylate	TAK-220
FLT	Nevirapine	Nelfinavir Mesylate	TNX-355
FLT	Nevirapine	Nelfinavir Mesylate	UK-427,857
FLT	Nevirapine	Ritonavir	Enfurvirtide
FLT	Nevirapine	Ritonavir	T-1249
FLT	Nevirapine	Ritonavir	AMD-070
FLT	Nevirapine	Ritonavir	BlockAide/CR
FLT	Nevirapine	Ritonavir	BMS 806
FLT	Nevirapine	Ritonavir	KRH-1636
FLT	Nevirapine	Ritonavir	ONO-4128
FLT	Nevirapine	Ritonavir	Pro-140
FLT	Nevirapine	Ritonavir	PRO-542
FLT	Nevirapine	Ritonavir	SCH-D
FLT	Nevirapine	Ritonavir	TAK-220
FLT	Nevirapine	Ritonavir	TNX-355
FLT	Nevirapine	Ritonavir	UK-427,857
FLT	Nevirapine	Saquinavir	Enfurvirtide
FLT	Nevirapine	Saquinavir	T-1249
FLT	Nevirapine	Saquinavir	AMD-070
FLT	Nevirapine	Saquinavir	BlockAide/CR
FLT	Nevirapine	Saquinavir	BMS 806
FLT	Nevirapine	Saquinavir	KRH-1636
FLT	Nevirapine	Saquinavir	ONO-4128

FLT	Nevirapine	Saquinavir	Pro-140
FLT	Nevirapine	Saquinavir	PRO-542
FLT	Nevirapine	Saquinavir	SCH-D
FLT	Nevirapine	Saquinavir	TAK-220
FLT	Nevirapine	Saquinavir	TNX-355
FLT	Nevirapine	Saquinavir	UK-427,857
FLT	Nevirapine	Tipranavir + Ritonavir	Enfurvirtide
FLT	Nevirapine	Tipranavir + Ritonavir	T-1249
FLT	Nevirapine	Tipranavir + Ritonavir	AMD-070
FLT	Nevirapine	Tipranavir + Ritonavir	BlockAide/CR
FLT	Nevirapine	Tipranavir + Ritonavir	BMS 806
FLT	Nevirapine	Tipranavir + Ritonavir	KRH-1636
FLT	Nevirapine	Tipranavir + Ritonavir	ONO-4128
FLT	Nevirapine	Tipranavir + Ritonavir	Pro-140

FLT	Nevirapine	Tipranavir + Ritonavir	PRO-542
FLT	Nevirapine	Tipranavir + Ritonavir	SCH-D
FLT	Nevirapine	Tipranavir + Ritonavir	TAK-220
FLT	Nevirapine	Tipranavir + Ritonavir	TNX-355
FLT	Nevirapine	Tipranavir + Ritonavir	UK-427,857
FLG	Nevirapine	Amprenavir	Enfurvirtide
FLG	Nevirapine	Amprenavir	T-1249
FLG	Nevirapine	Amprenavir	AMD-070
FLG	Nevirapine	Amprenavir	BlockAide/CR
FLG	Nevirapine	Amprenavir	BMS 806
FLG	Nevirapine	Amprenavir	KRH-1636
FLG	Nevirapine	Amprenavir	ONO-4128
FLG	Nevirapine	Amprenavir	Pro-140
FLG	Nevirapine	Amprenavir	PRO-542
FLG	Nevirapine	Amprenavir	SCH-D
FLG	Nevirapine	Amprenavir	TAK-220
FLG	Nevirapine	Amprenavir	TNX-355
FLG	Nevirapine	Amprenavir	UK-427,857

FLG	Nevirapine	Atazanavir	Enfurvirtide
FLG	Nevirapine	Atazanavir	T-1249
FLG	Nevirapine	Atazanavir	AMD-070
FLG	Nevirapine	Atazanavir	BlockAide/CR
FLG	Nevirapine	Atazanavir	BMS 806
FLG	Nevirapine	Atazanavir	KRH-1636
FLG	Nevirapine	Atazanavir	ONO-4128
FLG	Nevirapine	Atazanavir	Pro-140
FLG	Nevirapine	Atazanavir	PRO-542
FLG	Nevirapine	Atazanavir	SCH-D
FLG	Nevirapine	Atazanavir	TAK-220
FLG	Nevirapine	Atazanavir	TNX-355
FLG	Nevirapine	Atazanavir	UK-427,857
FLG	Nevirapine	Indinavir Sulfate	Enfurvirtide
FLG	Nevirapine	Indinavir Sulfate	T-1249
FLG	Nevirapine	Indinavir Sulfate	AMD-070
FLG	Nevirapine	Indinavir Sulfate	BlockAide/CR
FLG	Nevirapine	Indinavir Sulfate	BMS 806
FLG	Nevirapine	Indinavir Sulfate	KRH-1636
FLG	Nevirapine	Indinavir Sulfate	ONO-4128
FLG	Nevirapine	Indinavir	Pro-140

		Sulfate	
FLG	Nevirapine	Indinavir Sulfate	PRO-542
FLG	Nevirapine	Indinavir Sulfate	SCH-D
FLG	Nevirapine	Indinavir Sulfate	TAK-220
FLG	Nevirapine	Indinavir Sulfate	TNX-355
FLG	Nevirapine	Indinavir Sulfate	UK-427,857
FLG	Nevirapine	Lexiva	Enfurvirtide
FLG	Nevirapine	Lexiva	T-1249
FLG	Nevirapine	Lexiva	AMD-070
FLG	Nevirapine	Lexiva	BlockAide/CR
FLG	Nevirapine	Lexiva	BMS 806
FLG	Nevirapine	Lexiva	KRH-1636
FLG	Nevirapine	Lexiva	ONO-4128
FLG	Nevirapine	Lexiva	Pro-140
FLG	Nevirapine	Lexiva	PRO-542
FLG	Nevirapine	Lexiva	SCH-D
FLG	Nevirapine	Lexiva	TAK-220
FLG	Nevirapine	Lexiva	TNX-355
FLG	Nevirapine	Lexiva	UK-427,857
FLG	Nevirapine	Lopinavir + Ritonavir	Enfurvirtide
FLG	Nevirapine	Lopinavir	T-1249

		+ Ritonavir	
FLG	Nevirapine	Lopinavir + Ritonavir	AMD-070
FLG	Nevirapine	Lopinavir + Ritonavir	BlockAide/CR
FLG	Nevirapine	Lopinavir + Ritonavir	BMS 806
FLG	Nevirapine	Lopinavir + Ritonavir	KRH-1636
FLG	Nevirapine	Lopinavir + Ritonavir	ONO-4128
FLG	Nevirapine	Lopinavir + Ritonavir	Pro-140
FLG	Nevirapine	Lopinavir + Ritonavir	PRO-542
FLG	Nevirapine	Lopinavir + Ritonavir	SCH-D
FLG	Nevirapine	Lopinavir + Ritonavir	TAK-220
FLG	Nevirapine	Lopinavir +	TNX-355

		Ritonavir	
FLG	Nevirapine	Lopinavir + Ritonavir	UK-427,857
FLG	Nevirapine	Nelfinavir Mesylate	Enfurvirtide
FLG	Nevirapine	Nelfinavir Mesylate	T-1249
FLG	Nevirapine	Nelfinavir Mesylate	AMD-070
FLG	Nevirapine	Nelfinavir Mesylate	BlockAide/CR
FLG	Nevirapine	Nelfinavir Mesylate	BMS 806
FLG	Nevirapine	Nelfinavir Mesylate	KRH-1636
FLG	Nevirapine	Nelfinavir Mesylate	ONO-4128
FLG	Nevirapine	Nelfinavir Mesylate	Pro-140
FLG	Nevirapine	Nelfinavir Mesylate	PRO-542
FLG	Nevirapine	Nelfinavir Mesylate	SCH-D
FLG	Nevirapine	Nelfinavir Mesylate	TAK-220
FLG	Nevirapine	Nelfinavir Mesylate	TNX-355
FLG	Nevirapine	Nelfinavir Mesylate	UK-427,857

FLG	Nevirapine	Ritonavir	Enfurvirtide
FLG	Nevirapine	Ritonavir	T-1249
FLG	Nevirapine	Ritonavir	AMD-070
FLG	Nevirapine	Ritonavir	BlockAide/CR
FLG	Nevirapine	Ritonavir	BMS 806
FLG	Nevirapine	Ritonavir	KRH-1636
FLG	Nevirapine	Ritonavir	ONO-4128
FLG	Nevirapine	Ritonavir	Pro-140
FLG	Nevirapine	Ritonavir	PRO-542
FLG	Nevirapine	Ritonavir	SCH-D
FLG	Nevirapine	Ritonavir	TAK-220
FLG	Nevirapine	Ritonavir	TNX-355
FLG	Nevirapine	Ritonavir	UK-427,857
FLG	Nevirapine	Saquinavir	Enfurvirtide
FLG	Nevirapine	Saquinavir	T-1249
FLG	Nevirapine	Saquinavir	AMD-070
FLG	Nevirapine	Saquinavir	BlockAide/CR
FLG	Nevirapine	Saquinavir	BMS 806
FLG	Nevirapine	Saquinavir	KRH-1636
FLG	Nevirapine	Saquinavir	ONO-4128
FLG	Nevirapine	Saquinavir	Pro-140
FLG	Nevirapine	Saquinavir	PRO-542
FLG	Nevirapine	Saquinavir	SCH-D
FLG	Nevirapine	Saquinavir	TAK-220
FLG	Nevirapine	Saquinavir	TNX-355
FLG	Nevirapine	Saquinavir	UK-427,857

FLG	Nevirapine	Tipranavir + Ritonavir	Enfurvirtide
FLG	Nevirapine	Tipranavir + Ritonavir	T-1249
FLG	Nevirapine	Tipranavir + Ritonavir	AMD-070
FLG	Nevirapine	Tipranavir + Ritonavir	BlockAide/CR
FLG	Nevirapine	Tipranavir + Ritonavir	BMS 806
FLG	Nevirapine	Tipranavir + Ritonavir	KRH-1636
FLG	Nevirapine	Tipranavir + Ritonavir	ONO-4128
FLG	Nevirapine	Tipranavir + Ritonavir	Pro-140
FLG	Nevirapine	Tipranavir + Ritonavir	PRO-542
FLG	Nevirapine	Tipranavir + Ritonavir	SCH-D
FLG	Nevirapine	Tipranavir	TAK-220

		+ Ritonavir	
FLG	Nevirapine	Tipranavir + Ritonavir	TNX-355
FLG	Nevirapine	Tipranavir + Ritonavir	UK-427,857

Table 5 illustrating combinations of a compound of the formula (I), nevirapine, a protease inhibitor, an integrase inhibitor and optionally one, two or more further NRTIs

1st compound	2nd compound	3rd compound	4th compound
FLT	Nevirapine	Amprenavir	L-870810
FLT	Nevirapine	Amprenavir	c-2507
FLT	Nevirapine	Amprenavir	S(RSC)-1838
FLT	Nevirapine	Atazanavir	L-870810
FLT	Nevirapine	Atazanavir	c-2507
FLT	Nevirapine	Atazanavir	S(RSC)-1838
FLT	Nevirapine	Indinavir Sulfate	c-2507
FLT	Nevirapine	Indinavir Sulfate	S(RSC)-1838
FLT	Nevirapine	Indinavir Sulfate	L-870810
FLT	Nevirapine	Lexiva	c-2507
FLT	Nevirapine	Lexiva	L-870810

FLT	Nevirapine	Lexiva	S(RSC)-1838
FLT	Nevirapine	Lopinavir + Ritonavir	L-870810
FLT	Nevirapine	Lopinavir + Ritonavir	c-2507
FLT	Nevirapine	Lopinavir + Ritonavir	S(RSC)-1838
FLT	Nevirapine	Nelfinavir Mesylate	L-870810
FLT	Nevirapine	Nelfinavir Mesylate	c-2507
FLT	Nevirapine	Nelfinavir Mesylate	S(RSC)-1838
FLT	Nevirapine	Ritonavir	L-870810
FLT	Nevirapine	Ritonavir	c-2507
FLT	Nevirapine	Ritonavir	S(RSC)-1838
FLT	Nevirapine	Saquinavir	L-870810
FLT	Nevirapine	Saquinavir	c-2507
FLT	Nevirapine	Saquinavir	S(RSC)-1838
FLT	Nevirapine	Tipranavir + Ritonavir	L-870810
FLT	Nevirapine	Tipranavir + Ritonavir	c-2507
FLT	Nevirapine	Tipranavir	S(RSC)-1838

		+ Ritonavir	
FLG	Nevirapine	Amprenavir	L-870810
FLG	Nevirapine	Amprenavir	c-2507
FLG	Nevirapine	Amprenavir	S(RSC)-1838
FLG	Nevirapine	Atazanavir	L-870810
FLG	Nevirapine	Atazanavir	c-2507
FLG	Nevirapine	Atazanavir	S(RSC)-1838
FLG	Nevirapine	Indinavir Sulfate	c-2507
FLG	Nevirapine	Indinavir Sulfate	S(RSC)-1838
FLG	Nevirapine	Indinavir Sulfate	L-870810
FLG	Nevirapine	Lexiva	c-2507
FLG	Nevirapine	Lexiva	L-870810
FLG	Nevirapine	Lexiva	S(RSC)-1838
FLG	Nevirapine	Lopinavir + Ritonavir	L-870810
FLG	Nevirapine	Lopinavir + Ritonavir	c-2507
FLG	Nevirapine	Lopinavir + Ritonavir	S(RSC)-1838
FLG	Nevirapine	Nelfinavir Mesylate	L-870810

FLG	Nevirapine	Nelfinavir Mesylate	c-2507
FLG	Nevirapine	Nelfinavir Mesylate	S(RSC)-1838
FLG	Nevirapine	Ritonavir	L-870810
FLG	Nevirapine	Ritonavir	c-2507
FLG	Nevirapine	Ritonavir	S(RSC)-1838
FLG	Nevirapine	Saquinavir	L-870810
FLG	Nevirapine	Saquinavir	c-2507
FLG	Nevirapine	Saquinavir	S(RSC)-1838
FLG	Nevirapine	Tipranavir + Ritonavir	L-870810
FLG	Nevirapine	Tipranavir + Ritonavir	c-2507
FLG	Nevirapine	Tipranavir + Ritonavir	S(RSC)-1838

Table 6 illustrating combinations of a compound of the formula (I), nevirapine and a further antiviral

1st compound	2nd compound	3rd compound	4th compound
FLT	Nevirapine	PA-457	
FLT	Nevirapine	KPC-2	
FLT	Nevirapine	HGTV-43	
FLT	Nevirapine	Delavirdine	

FLT	Nevirapine	Efavirenz	
FLT	Nevirapine	(+)-Calanolide A or B	
FLT	Nevirapine	Capravirine	
FLT	Nevirapine	GW-695634	
FLT	Nevirapine	MIV-150	
FLT	Nevirapine	MV026048	
FLT	Nevirapine	NV-05	
FLT	Nevirapine	R-278474	
FLT	Nevirapine	RS-1588	
FLT	Nevirapine	TMC-120/125	
FLT	Nevirapine	TMC-125	
FLT	Nevirapine	UC-781	
FLT	Nevirapine	YM-215389	
FLG	Nevirapine	PA-457	
FLG	Nevirapine	KPC-2	
FLG	Nevirapine	HGTV-43	
FLG	Nevirapine	Delavirdine	
FLG	Nevirapine	Efavirenz	
FLG	Nevirapine	(+)-Calanolide A or B	
FLG	Nevirapine	Capravirine	
FLG	Nevirapine	GW-695634	
FLG	Nevirapine	MIV-150	
FLG	Nevirapine	MV026048	

FLG	Nevirapine	NV-05	
FLG	Nevirapine	R-278474	
FLG	Nevirapine	RS-1588	
FLG	Nevirapine	TMC-120/125	
FLG	Nevirapine	TMC-125	
FLG	Nevirapine	UC-781	
FLG	Nevirapine	YM-215389	

In the above given Tables 1 to 6 the term "FLG" is 2',3'-dideoxy-3'-fluoroguanosine, or a pharmaceutically acceptable salt or prodrug thereof, in particular 3'-deoxy-3'-fluoro-5-O-[2-(L-valyloxy)-propionyl]guanosine, or a pharmaceutically acceptable salt thereof.